REMARKS

Claims 15, 19, 21 and 23 have been cancelled without prejudice to presentation in a subsequent continuation application and claims 1, 13, 14, 20 and 22 have been amended. Claims 1-14, 16-18, 20, 22 and 24 remain in this application. The amendments to the claims have been made to further prosecution. No new matter has been added.

Support for the amendments to claim 1 can be found in the application and claims as filed and at least on pages 10-18 and Tables 1-6. Support for the amendments to claim 13 can be found at least at page 23, lines 12-14 and 26-28. Support for the amendment to claim 22 can be found at least at page 10, lines 7-14.

Objections to the Specification

Applicant respectfully points out that the informalities listed on page 5, line 18 and page 22, line 7, recognized as typographical errors, were corrected in amendments to the specification in the Response filed March 30, 2004. The amendments were entered and the objection to the specification was withdrawn in the Office Action dated 6/28/2004 (page 2, paragraph 1). Re-raising an objection that has previously been addressed successfully and withdrawn is unwarranted. Reconsideration of the objection is requested.

Claim Rejections

Claim Rejection Under 35 U.S.C. § 112, Second Paragraph

Claims 1-12 stand rejected under 35 U.S.C. § 112, second paragraph. Claim 1 is currently amended to add the phase "in the peripheral circulation" at the end of the claim, as suggested in the Office Action dated February 7, 2006. Applicant respectfully requests that this rejection be withdrawn.

Claim Rejection Under 35 U.S.C. § 112, First Paragraph

Claims 13, 14, 16-18, 20, 22 and 24 stand rejected under 35 U.S.C. § 112, first paragraph. Claim 13 is currently amended to delete the word "preventing" and substitute "treating." Support for "treating" can be found generally in the application as filed, and at least at page 1, line 12 and page 26, line 29. Applicant respectfully requests that this rejection be withdrawn.

Claim Rejections Under 35 U.S.C. § 103 (a)

Claims 1-14, 16-18, 20, 22 and 24 stand rejected under 35 USC § 103(a) as being unpatentable over Nawrocki et al. (*Transplantation Proceedings*, 28: 3538-3539, 1996) taken with Cramer et al. (*Transplantation Proceedings*, 29: 616, 1997) and Schmid et al. (*Eur. Surg. Res.*, 30: 61-68, 1998) and further in view of Kouwenhoven et al (*Transplant Int.* 13:385-401, 2000).

The claimed invention is directed to a method of ameliorating chronic allograft rejection in a human or animal allograft recipient comprising administering to the recipient in need of such treatment, in combination, a therapeutically effective amount of cyclosporin (CsA) at least once weekly and a therapeutically effective amount of 2-chlorodeoxyadenosine at least once weekly, wherein the administration results in a decrease in cell-mediated immune responses including decreased numbers of CD8+ T cells in the peripheral circulation (claim 1, currently amended). In another embodiment, the claimed invention is directed to a method of treating chronic allograft rejection in an allograft recipient comprising administering to an allograft recipient a therapeutically effective amount of cyclosporin at least once weekly and a therapeutically effective amount of 2-chlorodeoxyadenosine at least once weekly, wherein the administration results in a decrease in cell-mediated immune responses including decreased numbers of CD8+ T cells in the peripheral circulation (claim 13, currently amended).

None of the cited references discloses or suggests the administration of a therapeutically effective amount of cyclosporin in combination a therapeutically effective amount of 2-chlorodeoxyadenosine to produce a decrease in cell-mediated immune responses as indicated by decreased numbers of CD8+ T cells in the peripheral circulation. Therefore, the cited references, alone or in combination, do not disclose or suggest the present claimed invention, and the rejection of claims 1-14, 16-18, 20, 22 and 24 under 35 USC § 103(a) is unwarranted. The Applicant respectfully requests that the rejection be withdrawn and the claims proceed to issue.

The cited references that disclose the use of cyclosporin and 2-CdA in combination focus on the problem of acute allograft rejection. This focus is highlighted in the introduction (first paragraph) of the Nawrocki et al. article which states "Graft rejection has been the main problem in transplantation since the beginning. This reaction is due to differences in histocompatibility

antigens between the donor and organ recipient". In fact, review articles, written at the time the invention was made discuss the etiology and pathology of chronic graft rejection and emphasize: "there is still no treatment to inhibit or prevent CTD [chronic transplant dysfunction], and a conclusive therapeutic strategy is not within hand's reach since its etiology and patho-physiology are poorly known". Kouwenhoven et al., Etiology and pathophysiology of chronic transplant dysfunction, *Transplant Int.* 13:385-401, 387 (2000) at 386, of record. The Office Action dated February 7, 2006 makes the following statement:

> Further, with respect to the limitation of the effect of cellular immune responses, specifically decreasing the levels of circulatory CD8+ T cells as currently amended in claims 1 and 13; the reference of Kouwenhoven et al on page 392, right column teaches that the recognition of histoincompatible MHC alloantigens will provide an alloimune response. In allorecognition, the MHC antigen is bound to the T cell receptor, wherein once the CD4+ cell is activated, a cascade of events amplifies the alloimune response which leads to clonal proliferation of alloreactive cells and stimulates CD8+ T cells to develop into mature cytotoxic effector cells which are cytotoxic to the graft cells. Therefore, in view of the above, one of ordinary skill in the art by administering compounds and/or agents that ameliorate and/or treat chronic allograft rejection would expect to produce a decrease in cell-mediated immune responses including decreased circulating levels of CD8+ T cells in the peripheral circulation.
>
> Therefore, for the reasons discussed in the previous Office Action and in view of the above, the combined teachings of the prior art makes obvious a method of ameliorating or preventing the chronic allograft rejection by administering effective amount of cyclosporin in combination with 2-CDA and a pharmaceutical formulation for administration thereof including the limitations as currently amended in claims 1 and 13.

Applicant respectfully submits that the above statement is conclusory unsupported by evidence, an *ad hoc* reconstruction of prior art guided by the present claims and hindsight. Evidence is presented below to support this position.

First, the claim limitation is simply "decreased circulating levels of CD8+ T cells in the peripheral circulation." It is improper to read further characterizations of these T cells into the claims such as "cytotoxic" or "alloreactive." Second, a decrease or increase in circulating levels

of CD8+ T cells in the peripheral circulation does not in itself lead to a suggestion of the present invention using a combination of an effective amount of cyclosporin and effective amount with 2-CDA. The prior art in the area of allograft maintenance recognized that alloreactive CD8+ T cells deleted during tolerance induction slowly returned towards pretreatment levels, and further that the level of that alloreactive CD8+ T cells alone was not a predictor of allograft rejection. Iwakoshi, N.N., et al., Skin allograft maintenance in a new synchimeric model system of tolerance, *J Immunol.* 2001 Dec 1;167(11):6623-30, submitted with the Supplementary Information Disclosure Statement of August 7, 2006. This study concluded that the maintenance of healed-in allografts their model was a dynamic process dependent on 1) anti-CD154 mAb concentration, 2) CD4+ regulatory cells, and 3) activated alloreactive CD8+ thymic emigrants that have repopulated the periphery after tolerization. Iwakoshi, et al., 2001, page 6629, right-hand column, last paragraph.

A proper characterization of the scope and content of the prior art does not support the contention above that "one of ordinary skill in the art by administering compounds and/or agents that ameliorate and/or treat chronic allograft rejection would expect to produce a decrease in cell-mediated immune responses including decreased circulating levels of CD8+ T cells in the peripheral circulation." It was known at the time that the conventional immunosuppressive agents such as cyclosporin did not necessarily act in concert with, and in some situations antagonized, agents that block the co-stimulatory signals essential for T-cell activation. Adams, A.B., et al., Conventional immunosuppression and co-stimulation blockade, Philos Trans R Soc Lond B Biol Sci. 2001 May 29;356(1409):703-5, submitted with the Supplementary Information Disclosure Statement of August 7, 2006. Another study reported that calcineurin inhibitors, such as cyclosporin, could abrogate the effects of single dose of anti-CD154 co-stimulatory blockade, and that cyclosporin added to anti-CD154 therapy at a period about one month post-transplantation promoted the development of chronic allograft vasculopathy. See Sho, M., et al., New insights into the interactions between T-cell costimulatory blockade and conventional immunosuppressive drugs. Ann Surg. 2002 Nov;236(5):667-75, page 673, middle of left hand column and abstract, emphasis added, submitted with the Supplementary Information Disclosure Statement of August 7, 2006.

The case law addressing the requirements for establishing a *prima facie* 35 USC § 103(a) rejection is well settled. In particular, establishing a *prima facie* case of obviousness under 35 USC § 103(a) requires that each of three requirements must be met. First, the references, taken alone or in combination, must teach or suggest each and every element recited in the claims. See M.P.E.P. § 2143.03 (8th ed. Rev. 1, Feb. 2003) citing In re Royka, 490 F. 2d 981, 180 USPQ 580 (CCPA 1974). Second, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to combine the references in a manner resulting in the claimed invention. And third, a reasonable expectation of success must exist. Furthermore, each of these requirements must "be found in the prior art, and not be based on applicant's disclosure." M.P.E.P. § 2143 (8th ed. Rev. 1, Feb. 2001). Determinations of *prima facie* obviousness must be supported by a finding of "substantial evidence." *See* In re Zurko, 258 F. 3d 1379, 1386 (Fed. Cir. 2001). Specifically, unless "substantial evidence" is found in the record that supports the factual determinations central to the issue of patentability, including motivation, the rejection is improper and should be withdrawn. Substantial evidence is something less than the weight of the evidence but more than a mere scintilla of evidence. In re Kotzab, 217 F.3d 1365, 1369, 55 U.S.P.Q.2d 1313 (Fed. Cir. 2000). In this case, there is no "substantial evidence" in the record to support the characterization of the prior art and the combinations alleged by the Examiner, nor is there the requisite "clear and particular" motivation required to support a *prima facie* case of obviousness.

The Patent and Trademark Office has the burden under section 103 to establish a *prima facie* case of obviousness. In re Fine, 837 F.2d 1071, 1074, 5 U.S.P.Q2d 1596 (Fed. Cir. 1988). It can satisfy this burden only by showing some objective teaching in the prior art or that knowledge generally available to one of ordinary skill in the art would lead that individual to combine the relevant teachings of the references. Id. Until the Office has met the burden to establish a *prima facie* case of obviousness, the burden of rebutting that case does not shift to the Applicant.

The Applicant respectfully submits that the Patent and Trademark Office has not borne the burden to establish a *prima facie* case of obviousness, and requests that all rejections under 35 USC § 103 (a) be withdrawn.

With regards to the variation of dosage, at best, the Office Action is advancing an "obvious to try" argument. "An 'obvious-to-try' situation exists when a general disclosure may pique the scientist's curiosity, such that further investigation might be done as a result of the disclosure, but the disclosure itself does not contain a sufficient teaching of how to obtain the desired result, or that the claimed result would be obtained if certain directions were pursued." In re Eli Lily & Co., 902 F.2d, 943, 945 (Fed Cir. 1990). However, "obvious to try is not the standard," what is required is a "reasonable expectation of success". In re O'Farrell, 853 F.2d 894, 904, (Fed. Cir.1988).

Claims 1-14, 16-18, 20, 22 and 24 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Nawrocki et al. taken with Cramer et al. and Schmid et al. and further in view of Kouwenhoven et al. For the reasons discussed above, the Applicant believes that this rejection is moot in view of the present amendments; withdrawal of the rejection is respectfully requested.

CONCLUSION

In light of the amendments and arguments presented herein, the Applicant respectfully requests reconsideration and a timely Notice of Allowance to follow in this case. The Applicant requests that the Examiner telephone the undersigned at (508) 929-1658 in the event a telephone discussion would be helpful in advancing the prosecution of the present case.

Respectfully submitted,

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